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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,681	11/23/1999	JACK A. ROTH	INRP.003--2/	4103

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	25

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/447,681	ROTH, JACK A.	
	Examin r	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this c mmunication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67 and 86-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67 and 86-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 November 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 30, 2003 has been entered.

As applicant has filed terminal disclaimer over US patent application 09/668,532 (now US Patent 6,511,847) and US Patent 6,410,010, the obviousness-type double patenting rejections have been overcome.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 67 and claims 86-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as set forth in the office action mailed September 27, 2002 in paper no. 19.

The instant specification does not contemplate adenoviral vectors comprising a wild type p53 gene operably linked to a promoter, nor does the specification contemplate the specific embodiments where the promoter is a CMV, RSV, β-actin or SV40 promoter. Thus, the specification does not provide evidence that Applicant had possession of the claimed invention at the time of filing.

The specification has been read in its entirety and the examiner has not been able to determine support that would satisfy the written description portion of 35 USC §112.

Further, a reading of the specific citations indicated by Applicant in the preliminary amendment filed November 23, 1999 to support the present claims, reveals that support is not found at these citations. At page 7, lines 1-7, there is discussion of evidence in the art that mutations of the p53 gene cause lung cancer; page 9, line 6-8, states that the vector construct for introducing a wild type p53 gene under the control of a β-actin promoter is a retroviral vector; page 9, lines 14-15, discusses in general wild type p53 constructs; page 14, lines 26-27 and 31-34, discusses antisense RNA expressed from any promoter; page 15, lines 1-5, state that the β-actin, RSV, SV40 and a CMV promoters are used to express antisense RNA; page 25, lines 4-5, discuses that mutations of a p53 gene are the most frequently found mutations in human cancers; page 26, lines 13-16, states that the inventors feel that the reversal of a single altered genetic event in a cancer cells can potential reverse critical features of the malignant phenotype; page 27, lines 24-28, states that the protocol focuses on the regional delivery of wild type p53 for the treatment of tumors; page 33, lines 9-11, states that adenovirus can be used to introduce an antisense intron; and page 66, lines 10-18, states that tumors should be resected and that to the residual tumor the appropriate retroviral vector is to be injected. Further, the examiner has found at page 63, lines 30-34, a statement that antisense p53 in a retrovirus is used; page 64, lines 27-31, states a retroviral construct comprising p53 cDNA; page 65, lines 7-22, states retrovirus mediated transfer of p53 cDNA and pages 67, line 15 to page 68, line 1, states risks of retroviruses. At no place in the specification is the invention of the claims clearly set forth so that the skilled artisan would realize that which Applicant perceived as their invention at the time of filing. In the places where adenovirus or the specific classes of promoters claimed are disclosed, each such disclosure is within the context of antisense RNA production. Therefore the specification lacks a written description of the invention as claimed.

MPEP 2163.02 states:

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Electronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

It is maintained that the present specification provides no such reasonable clarity to those skilled in the art that Applicant was in possession of the claimed invention. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. Applicant is denied benefit of the early priority dates claimed, as they do not provide a written description of the claimed invention. To be granted priority under 35 USC § 120, the claims must comply with 35 USC § 112, first paragraph. The specifications of 07/960,513, filed October 13, 1992 and 07/665,538, filed March 6, 1991 do not provide

written description for claimed adenoviral vectors. Therefore, applicant is given the priority date of November 23, 1999.

Applicant provides seven "bullets" that they feel support the enablement of the present claims. The examiner has read these seven bullets and does not agree with Applicant's reasoning and evidence. Applicant argues that:

1. At page 9, lines 6-12, the specification states generally "in one specific embodiment, the invention concerns vector constructs for introducing wild type p53 genes ..."; "... wherein the wt-p3 is placed under the control of the β-actin promoter, and the unit is positioned in reverse orientation into a retroviral vector." Therefore, this citation discloses a "specific embodiment" of a vector constructs for introducing wild-type p53 into cells, and states "these embodiments involve the preparation of a gene expression unit where the wt-p53 gene is placed under the control of the β-actin promoter, and the unit is positioned in a reverse orientation into a retroviral vector." In this discussion, the only contemplation is stated to be a retroviral vector having in reverse orientation a wt-p53 gene operatively linked to a promoter. There is no contemplation of an adenoviral vector comprising a CMV promoter, or any other specifically claimed promoter, operatively linked to a wt-p53 gene at this place in the specification. Without evidence of contemplation, there is no possession at the time of filing.

2. At page 61, lines 29-30, the only vector discussed to express wild type p53 in both orientations is a retroviral vector. There is no specific disclosure of adenovirus vectors at this citation, and thus there is no evidence provided here that applicant had possession of the claimed invention at the time of filing. Thus, this citation fails to provide the needed support for written description.

3. At page 8, line 25 or page 9, line 4, the effect which is stated to be achievable with other promoter/vector constructs, is the enhanced expression when the promoter in the retrovirus

is reversed with regard to other promoters within the retrovirus (page 8, lines 25-31). This citation discusses the discovery that when the selected promoter/gene construct is aligned within the vector in an orientation that is reversed with respect to direction of transcription with respect to other promoters with in the vector, a dramatic increase in transcription of the selected gene is seen. Then the passage goes on to discuss the use of retroviral vectors where the transcription of the selected gene is in reverse orientation to other retroviral transcription. The passage continues by stating that while the increase in transcription was observed using the β-actin promoter and retroviral vector, the inventors believe that the increase will be seen other promoter/vector constructs. The examiner will agree that Applicant has contemplated in general vectors having the gene of interest operatively linked to promoter, and having both in reverse orientation for transcription relative to transcription of other genes in the vector. However, the support for other than retrovirus does not support the species of adenovirus vector comprising a CMV promoter, or any other promoter. There is no evidence provided at this citation that applicant was in possession of the claimed subject matter at the time of filing.

4. At page 14, lines 21-23, are not seen as supporting written description. A reading of the specification from at least page 5, line 7 to at least page 16, line 10, shows that this citation is embedded in a paragraph discussing antisense technology. This citation does state that "in addition to retroviruses, it is contemplated that other vectors can be employed, including adenovirus ....". However, when read in context of the paragraph, one would realize that the adenovirus contemplated contains antisense sequences. The larger relevant citation (page 14, lines 9-25) states "in broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors .....", "although the retrovirus would inhibit the growth of the tumor, the expression of the antisense construct in non-tumor cells .....", "in addition to retroviruses, it is contemplated .... adenoviruses" .As discussed above the

entire paragraph, page 14, lines 9-25, contemplates only antisense. This only supports an adenoviral vector comprising an antisense construct and not the adenovirus of the claims. Thus, this citation fails to provide evidence of possession of the claimed invention at the time of filing.

5 and 6. At page 15, lines 1-4, and page 14, line 35 to page 15, line 2, each citation is embedded in a paragraph that begins "the particular promoter that is employed to control the expression of the antisense RNA ....". Furthermore, page 15, line 5 states that "while the β-actin promoter is preferred in the invention is by no means limited to this promoter, and one may also mention .....CMV." However, when the entire paragraph is read, "the invention" at this point is the expression of antisense sequences. Please refer to the paragraph at page 14, line 27 "the particular promoter that is employed to control the expression of the antisense RNA in a vector construct is not believed to be particularly crucial ..... where a human cell is targeted, it will be preferred to position the antisense RNA coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell ... generally speaking, such a promoter might include either a human cellular or viral promoter..... while the β-actin promoter is preferred .... CMV". Page 14, line 35 to page 15, line 2, states "generally speaking, such a promoter might include either a human cellular or viral promoter.....". However, when read in the full context, as discussed above (page 14, lines 21-23), the description is for "generally speaking" regarding promoters for use in retroviruses comprising antisense sequences, and not the claimed invention. A reading of the complete paragraph assigns the citation provided by Applicant to refer only to retrovirus vectors expressing antisense. There is no written support for the claimed invention.

7. At page 16, lines 5-10, the specification states "while the retrovirus construct aspect .... concerns the use of a β-actin promoter in reverse orientation, there is no limitation on the

nature of the selected gene ..."; "thus, the invention concerns the use of antisense coding constructs as well as "sense" constructs that encode a desired proteins. The contemplation is clearly for other genes expressed in the sense or antisense orientation from the β-actin promoter in a retroviral vector. The specification at this point does not discuss adenovirus as a contemplated vector, the CMV promoter as the contemplated promoter or wt-p53 as the contemplated gene. Thus, this citation fails to provide written description of the claimed invention.

The passages provided by Applicant do not provide the type of disclosure that would convey to the artisan that Applicant possessed the claimed invention at the time of filing. The are no passages that clearly provide written description of an adenovirus vector comprising a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter controlling a wt-p53 gene so that the artisan would realize that Applicant considered such as part of the invention at the time of filing.

Applicant argues that they provided during prosecution declarations from Dr. Lou Zumstein and Dr. Philip Hinds, both whom applicant defines as persons of ordinary skill in the art, in support of their allegations that the specification provides written description of the claimed invention. Applicant argues that evidence, as opposed to argument, should be required to meet the "preponderance of the evidence" standard in MPEP 2163.04. These arguments are not persuasive.

Both declarants Zumstein and Hinds used as their evidence citations from the specification. These citations both state provide the evidence that the specification provides written description of the claimed invention. The examiner's response used the same evidence as the declarants: the specification. In rebutting the statements made by both declarants, the examiner reviewed the specific citations indicated by the declarants and

made an argument as to why those citations did not support written description of the claimed invention. This type of rebuttal is permissible under MPEP 2163.04:

> When a rejection is maintained, any affidavits relevant to the 35 U.S.C. 112, parag. 1, written description requirement, must be thoroughly analyzed and discussed in the next Office action. See In re Alton, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

The examiner provided such a thorough analysis.

Applicant argues that adenoviruses are discussed in the application and states that such can be found at specification page 14, lines 9-12, which states "In broader aspects of the invention, a preferred approach will involve the preparation of retroviral vectors which incorporate nucleic acid sequence encoding the desired construct, once introduced into the cell to be treated ...". Applicant argues that the use of adenovirus is discussed in the context of "broader aspects of the invention". Applicant argues that retrovirus and antisense constructs are but examples of broader aspects of the invention. Applicant argues that the paragraph at page 14, line 35 to page 15, line 2 recites particular embodiments of the invention such as antisense, but the passage includes "Generally speaking, such a promoter might include either a human cellular of viral promoter..". These arguments are not persuasive.

The paragraph at page 14, lines 9-25, discusses the invention in terms of delivering antisense oligonucleotides to a cell using a retroviral vector. The mention of adenovirus in the last sentence of the paragraph, refers to the delivery of antisense oligonucleotides. When the paragraph at page 14, lines 9-25 are read in context, including paragraphs before an after the citation, it is clear that the delivery of antisense oligonucleotides is the topic. The paragraph at page 13, lines 23-43, discusses the application of antisense intron RNA either directly or indirectly to the cell (lined 25-26). The indirect form of application is by an antisense construct in the form of retroviral constructs (lines 26-28). The remainder of the

paragraph discusses the direct delivery of antisense RNA. The next paragraph, which is the one cited by Applicant, continues a discussion of delivery of the construct via a retroviral vectors, which incorporate the desired construct (page 14, lines 9-14). The discussion of construct here clearly refers back to the antisense construct in the preceding paragraph. This is further emphasized by statements made later in the paragraph that the retrovirus would inhibit growth of the tumor cell (page 14, lines 17-18). Then, the paragraph lists other vectors that could be used instead of retrovirus, adenovirus being one of them (page 14, lines 23-24). However, the clear contemplation is the delivery of antisense RNA by these other vectors, including adenovirus. The paragraph bridging pages 14 and 15, is "generally speaking" about promoters for the antisense constructs. The sentence just prior to Applicant's citation states "... it will be preferred to position the antisense RNA coding region adjacent to an under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include a human cellular or viral promoter." Thus, applicant's citation at page 14, line 35, when read in context, not only indicates that the human cellular and viral promoters are contemplated for expressing antisense RNA, it also adds support that the mention of adenovirus in the preceding paragraph is in the context of expressing antisense RNA and not wild-type p53 or any sense construct.

Therefore, none of applicant's nor declarants citations or arguments thereof provides for written description of an adenoviral vector comprising a wild-type p53 gene at the time of filing. As applicant cannot possess what has not been described, applicant has not shown possession of the claimed invention at the time of filing.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67 and 86 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Liu et al (1994) Cancer Res. 54, pages 3662-3667.

Lui teaches an adenovirus vector comprising a wild-type p53 gene operably linked to an CMV promoter (page 3662, col. 2, parag. 4). Thus, Lui clearly anticipates the claimed invention.

Applicant argues that their earliest priority date is October 13, 1992, and thus Lui is a post filing publication and is not available as a prior art document. This argument is not persuasive.

For the reasoning presented above, applicant's are not due benefit of their earlier filing dates because the specification lacks written description for the claimed invention. As applicant has been given a priority date of November 23, 1999. This later filing date makes Lui an available reference.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (1990) Science 250, 1576-1579 and Stratford-Perricaudet et al (1990) Human Gene Therapy 1, 241-256 in view of Wilkinson et al (1992) Nucleic Acids Res. 20, 2233-2239, Colicos et al (1991) Carcinogenesis 12, 249-255, Rajan et al (1991) J. Virol. 65, 6553-6561 and Hitt et al (1990) Virol. 179, 667-678.

Claims 86-89 are drawn to adenovirus vectors comprising a wild type p53 gene or a human wild type p53 gene under the control of a promoter, where the promoter can be a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter.

Chen et al teach retroviral vectors comprising a wild type human p53 operably linked to the retroviral LTR (page 1576, col. 3, Figure 1). Chen et al teach that wild type 53 is expressed in transduced Saos cells, and that the transduced cells failed to form colonies on soft agar or tumors in nude mice (page 1577, col. 2, line 12 to col. 3, line 8). Chen et al also teach that wild type p53 counters the transformation phenotype conferred by a mutant p53 when both genes are present in equal gene dosage (page 1579, col. 1, parag. 1 to col. 2, line 1 and col. 2, parag. 1, lines 25-28). Stratford-Perricaudet et al teach the correction of an enzyme deficiency related disorder in mice (abstract). The mice are mutant for ornithine transcarbamylase and when treated with an adenovirus vector comprising an ornithine transcarbamylase DNA sequence operably linked to the adenovirus major late promoter, the mice exhibit a reversal of the mutant phenotype (page 251, parag. 1, lines 1-3). Chen et al and Stratford Perricaudet et al do not teach adenoviral vectors comprised of a wild type p53 gene under the control of a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter. Wilkinson et al teach the production of an adenovirus expression system where a CMV promoter regulates expression of lacZ (page 2234, col. 1, parag. 5, lines 1-3). Wilkinson et al also teach that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). Colicos et al teach an adenovirus vector comprising a T4 *denV* gene operably linked to the RSV promoter, the RSV LTR (page 250, col. 1, parags. 4-7, figure 1 and figure 2). The vector, Ad5denV, was shown to partially complement the excision repair deficiency in primary fibroblasts from xeroderma pigmentosa patients (page 254, col. 1, parag. 2, and page 253, figures 6 and 7, and Table 1). Rajan et al teach an adenoviral vector comprising a

cDNA sequence encoding an SV 40 small-t antigen operably linked to an SV40 promoter (page 6554, col. 1, parag. 2). Rajan et al teach that the expression of the SV40 small-t antigen results in the transactivation of adenovirus EII early promoter (page 6557, col. 1, line 13 to col. 2, line 4). Hitt et al teach an adenovirus where the expression of the E1A gene is regulated by a human β-actin promoter (page 670, col. 1, line 12 to col. 2, line 2, and figure 1). Hitt et al teach that E1A production is 3 to 5 times higher than by wild type adenovirus (page 675, col. 2, parag. 1, lines 11-16).

Thus it would have been obvious to the ordinary artisan at the time of the instant invention to determine the reversal of a transformed phenotype by expressing in an adenoviral vector comprising a human wild type p53 gene operably linked to a promoter, and specifically where the promoter is a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter, given the teachings of Chen et al that wild type p53 can reverse the transformed phenotype of tumor cells when the cells are transduced with a retroviral vector comprising a human wild type p53 gene operably linked to a promoter and the teachings of Stratford-Perricaudet et al that adenoviruses are useful for human gene therapy protocols in view of the teachings of Wilkinson et al, Colicos, Rajan et al or Hitt et al that a CMV promoter, a β-actin promoter, an SV40 promoter or an RSV promoter functions within a adenovirus to regulate expression of a sequence encoding a protein of interest. All that is required that there is a reasonable expectation of success and motivation to make the claimed adenovirus vectors. Motivation is provided by Chen et al in stating that expression of p53 in cells Saos cells which lack functional p53 reverts the transformed phenotype, and that such suggests possible clinical use of p53 gene replacement (page 1579, col. 1, parag. 1, line 1 to col. 2, line 1 and col. 2, lines 21-25). Additional motivation comes from Stratford-Perricaudet et al offer that states that adenoviral vectors can be used in human gene therapy procedures to restore impaired metabolism (abstract, last line).

Thus, it would have been obvious to the ordinary artisan at the time of the present invention, to produce the claimed vectors for assessment of their in vivo expression potential. Promoter testing was known within the art at the time of filing to determine those promoters that provided the best expression.

Applicant argues that the combination of references in the previous office action do not provide the requisite teachings, motivation or suggestions required for obviousness. Applicant argues that the courts have stated that the mere fact that a combination or modification of a reference or references is possible is not sufficient for obviousness. Applicant argues that the prior art must also suggest the desirability of the combination that is the art must provide the motivation. Applicant argues that the suggestion or motivation to combine is particularly true given the absence of evidence in Chen and Wilkinson for using adenovirus in a therapeutic context and the limited success of the Stratford-Perricaudet reference report when adenovirus was used. Applicant argues that the Chen reference mentions replacing mutated tumor suppressors with wild-type versions, which is possible with retrovirus but not possible with adenovirus as they do not integrate. Applicant that there is no suggestion in any of the cited references to substitute the retroviral vector of Chen with the adenoviral vector of Stratford-Perricaudet. Applicant argues, with regards to Stratford-Perricaudet, that the reference teaches that in one of two animals tested long-term expression of OTC was not observed., and that OTC activity was not significantly altered. Applicant argues that Stratford-Perricaudet teaches that the defect was only partially changed, without a resulting phenotypic change to the animals. Applicant argues that this would not provide motivation to use an adenovirus vector. Applicant argues that the production of a replication defective adenovirus – p53 construct would be even more difficult since overexpression of p53 is needed to mediated cell death. These arguments are not persuasive.

Pro-Mold Tool Co. v. Great Lakes Plastics Inc. 75 F.3d 1568, 1573, 37 USPQ2d 1626,1629 (Fed. Cir 1996). We note that: reason, suggestion, or motivation to combine two or more prior art references in single invention may come from references themselves, from knowledge of those skilled in art that certain references or disclosures in references are known to be of interest in particular field, or from nature of problem to be solved. This applicant is incorrect in stating that motivation must come directly from the cited references. However, the examiner maintains that there is sufficient motivation in making a Ad-p53 construct, a product. At this point the examiner would like to state that the claimed invention is to a particular adenoviral construct and not a method of using the construct in a method of treatment. Further, Stratford-Perricaudet teaches that mutant mice, treated with Ad-MLP-OTC showed an increase in hepatic OTC production, as compared to untreated mutant mice, that lasted at least in one mouse for 13 months (bridge. parag. page 251-252). Further, Stratford-Perricaudet state that the sparse fur phenotype was diminished in the treated mutant mice and that urine erotic acid levels declined (page 252, parag. 4 and 5). Thus, Stratford-Perricaudet does teach a meaningful phenotypic change associated with the expression of Ad-MLP-OTC. Applicant is incorrect in asserting that there was no phenotypic change. Further, the rejection is not based on a method of therapy, but based on teachings, suggestions and motivations found in the art and general knowledge in the art to produce an adenoviral vector. Applicant, in arguing the effectiveness of the vectors in the art in therapeutic situations, is misplaced as the only teachings required, related to producing the vector. Further, Wilkinson teaches that the adenovirus-CMV system can be used to studies of gene expression and gene regulation (page 2238, col. 2, parag. 4, lines 1-4). The correction of the transformed phenotype in Saos cells by delivering a wild-type p53 gene in a retroviral vector, requires both gene expression and gene regulation. The claimed product, an adenoviral vector comprising a wild-type p53 gene operably linked to a

CMV promoter, is obvious over Chen in view of Wilkinson. Chen has taught a mutant cell - retroviral expression system in which gene expression and gene regulation is paramount. Wilkinson has taught an adenoviral expression system, and states that this system is useful for studying gene expression and gene regulation. When this is taken in view of Stratford-Perricaudet, the proposal for preparing an adenoviral vector comprising a CMV promoter operably linked to a wild-type p53 gene is obvious under the meaning of 103. Thus, the ordinary artisan would have found it obvious to take the mutant cell - retroviral expression system of Chen and substitute the adenoviral – CMV promoter of Wilkinson to study gene expression and gene regulation in Saos cells for further use of the vector in gene therapy protocols.

Applicant argues that at the time of filing, other references teach poor results and showed efficacy of adenovirus in a therapeutic context to be sketchy. Applicant argues that Rosenfeld (1992) demonstrated that the transfer of CFTR to pulmonary epithelium resulted in expression but no physiologic effect. Applicant argues that Rosenfeld (1991) also showed expression of α1-antitrypsin but no physiologic effect, and that Rosenfeld (1991) stated that the level of expression was expected to be less than that required for a physiologic effect. These arguments are not persuasive.

It is not clear what physiologic effects would be expected in the models used by both Rosenfeld (1991) and (1992). The cotton rats were wild type so the expression of either CFTR or α1-antitrypsin would not be expected to have an effect. In addition, the claims are to a vector and not a method of treatment. The level of expression is not seen as relevant for just the vector. The motivation to combine would come from the art know need for a vector that expressed sufficiently for a therapeutic benefit and Stratford-Perricaudet teaches that adenovirus does just that, and provides the motivation to combine for observing in vivo expression levels.

Applicant argues that Gaffe shows the introduction of the human α1-antitrypsin gene into the liver of normal rats by intraportal injection. Applicant argues that while Jaffee obtained measurable plasma levels in the rats, the overall expression level was insufficient to be therapeutic. Applicant argues that in situations that require the production of biologically significant levels of p53, use of adenovirus would have been questionable. Applicant argues that the use of adenovirus to deliver p53 in a therapeutic context would have lack the requisite motivation. These arguments are not persuasive.

What Jaffee, and Rosenfeld, teaches is that for methods of therapy, the administration of Ad-p53 would be unpredictable, not that the vector would not be obvious at the time of filing. Applicant has not shown that the artisan would have lacked a reasonable expectation of success at achieving the vector, not at achieving a therapeutic outcome of the vector. All of the claims are to a vector, not a method of using the vector.

Applicant argues that the specification of an application that claims priority to the present application teaches that p53 would be toxic to a packaging cell, and that adenovirus E1B protein binds to p53. These arguments are not persuasive.

If applicant is trying to establish a teaching away, the citation from the child application is not sufficient. In this instance, applicant needs to establish that the teaching is sufficiently negative that the ordinary artisan would not believe that Ad-p53 could not be made. The art believing the toxicity is not sufficient for a negative teaching. The binding of E1B to p53 and inactivating it is more of an issue with methods of treatment, and is a reason as to why the methods should be limited to E1B- adenoviral vectors. However, binding to p53 isn't sufficient to say the vector could not be made and used. If the presence of E1B is so deleterious that vector production is inhibited, applicant should limit their claim to an E1B- adenovirus.

Applicant argues that it is impermissible for the examiner to pick and chose from a reference only that which will support a given position to the exclusion of other parts necessary to the full appreciation of what such references fairly suggests to one skilled in the art.. This argument is not persuasive as there is no evidence of picking an choosing or what was excluded.

Applicant argues that the references of Colicos, Rajan and Hitt are cited for the use of an adenoviral vector comprising an RSV promoter, an SV40 promoter or a β-actin promoter, respectively. Applicant argues that each reference discloses an adenoviral vector with a promoter that does not drive expression of a p53 gene. Applicant argues that Chen does not motivate its combination with Wilkinson, Colicos, Rajan or Hitt, and that Wilkinson, Rajan or Hitt do not suggest combination with Chen (page 16, lines 4-7). These arguments are not persuasive.

Applicant argues that Wilkinson, Colicos, Rajan and Hitt teach away from the claimed invention because they fail to mention p53, and they discuss expression of other genes, none of which is a therapeutic gene. Applicant argues that several of the genes were thought to be responsible for cellular transformation.

Applicant's arguments might have greater bearing if Stratford-Perricaudet were not of record in the 103. Stratford-Perricaudet, as discussed above, teaches a successful gene therapy protocol where an adenoviral vector delivers a wild-type version of a mutant gene. The references of Wilkinson, Colicos, Rajan and Hitt each teach adenoviral vectors with, respectively, a gene of interest under the control of a CMV promoter, an RSV promoter, an SV40 promoter and a β-actin promoter. Furthermore, just because none of the secondary references teach the expression of a p53 gene, that is just because none of the secondary references are a 102-type reference, does not mean that the references teach away from the claimed invention. Further, whatever gene was being expressed in the secondary

references does not teach away because use of the references is based on what was being expressed. The rejection clearly indicates substituting the gene of the reference with p53, the gene of Chen. Additionally, teaching away from an invention or an obviousness rejection, means that the art cited provides reasoning or indicates that a particular combination would not function together. None of the cited references teach that an adenovirus of the claims could not function together.

Applicant argues that Stratford-Perricaudet states that the feasibility of using adenovirus for direct gene transfer is limited to enzyme encoding genes, and that p53 is not an enzyme. Applicant argues that the limited expression of OTC by the adenovirus vector used does not motivate the use of an Ad-p53 vector to treat cancer. These arguments are not persuasive.

The claims are to an adenovirus vector. The art taught adenovirus vectors as capable of expression in vivo and in vitro. For the production of an adenovirus vector of the claims, the art provides the teaching, suggestion and motivation. The purpose for making the vectors is not required to achieve a therapy, but can be only to observe expression in vivo or in vitro. If the claims were to methods of therapy, applicant's arguments would have greater merit.

Stratford provides the motivation to modify Chen, as Stratford-Perricaudet teaches the successful therapeutic production of OTC. The remaining references provide teachings of successful expression by the β-actin promoter, SV40 promoter and the RSV promoter. All is required is that there is a reasonable expectation of success in making these various vectors. There is no requirement that the vectors rise to the level of successful gene therapy.

Applicant argues that there must be a reasonable expectation of success in the therapeutic context that the examiner has relied upon. Applicant argues that Wilkinson,

Colicos, Rajan and Hitt are not relevant because they do not discuss the use of adenovirus in the context of a therapeutic gene. Applicant argues that the Stratford-Perricaudet, Rosenfeld (1991 and 1992) and Jaffee references make clear that the ordinary artisan at the time of filing would have expected very little of the claimed invention. Applicant argues that expression results were very poor, and that effective levels of expression for an enzyme were thought to be less that than for p53. These arguments are not persuasive.

Applicant has not understood the rejection. The examiner is not saying that the Ad-p53 vector is obvious for use in a gene therapy. Reversal of a transformed phenotype is not the same as therapy. For a therapy, the reversal would need to be sufficiently high to alter a disease symptom. In assessing the motivation, the examiner state that the combination of Chen and Stratford-Perricaudet would be obvious in view of Chen's teaching of a reversal of a transformed phenotype and Stratfort-Perricaudet's successful gene therapy. These are the teachings, suggestions and motivations, but the rejection does not state that the vector is to be used in gene therapy protocols. Rather, the use of adenovirus in gene therapy protocols would motivate the ordinary artisan at the time of filing to make the vectors and assess their in vivo expression, but that expression does not need to rise to a therapeutic outcome. The examiner has rewritten part of the obviousness rejection to remove confusion.

Applicant argues that the action provides the basis of an obvious to try. Applicant argues that the cited references fail to indicate that sufficient p53 expression could be achieved and thus is only obvious to try. This argument is not persuasive.

Applicant needs to further explain how the references make it obvious to try to produce the Ad-p53 vectors claimed. While the examiner might agree that would have been obvious to try at the time of filing to use the vectors in a method of therapy, the examiner

does not agree that it obvious to try to make the vectors and use them to determine in vivo expression potential.

Applicant argues that the invention lies in the area of unexpected results. Applicant argues that the invention is to Ad-p53 vectors in the context of gene therapy, and that the PTO has long espoused a view that gene therapy is an unpredictable area. Applicant provides an office action to support this argument. Applicant argues that gene therapy success constitutes a surprising and unexpected result that could not have been based on the prior art cited. Applicant argues that declarant Deborah R. Wilson provides evidence of surprising and unexpected efficacy in the treatment of many different types of cancer using INGN 201. Applicant argues that others provide evidence of success in use of INGN 20 to treat cancer. These arguments are not persuasive.

The declaration by Deborah R. Wilson has been reviewed and is deficient because the adenoviral construct that is INGN 201 is not disclosed. Further, while the references cited in support of applicant's arguments are evidence of unexpected results in gene therapy methods, it is not seen how this makes the vector itself an unexpected result. In addition, SC58500, the vector for which unexpected results is argued in several of the references, is an AD-CMV-p53 construct. As such, there is only a correlation in unexpected results, if there is an unexpected results with the vector as opposed to the methods, with the vector of claim 67. For claims 86-89, there is no such showing. As applicant has argued the unpredictability of gene therapy for any particular vector, the provided declaration and references do not provide unexpected results. "The evidence presented to rebut a prima facie case of obviousness must be commensurate in scope with the claims to which it pertains." See In re Dill, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979).

Further, the office action that applicant cites, appears to be addressing claims to methods of gene therapy, and not the vectors themselves. The present claims are to vectors and not methods.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
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